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Disturbed T Cell Signaling and Altered Th17 and Regulatory T Cell Subsets in the Pathogenesis of Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the presence of autoantibodies against nuclear components. Circulating immune complexes of chromatin and autoantibodies deposit in various tissues leading to inflammation and tissue damage. It has been well documented that autoimmunity in SLE depends on autoreactive T cells. In this review, we summarize the literature that addresses the roles of T cell signaling, and Th17 and regulatory T cells (Tregs) in the development of SLE. T cell receptor (TCR) signaling appears to be aberrant in T cells of patients with SLE. In particular, defects in the TCR ζ chain, Syk kinase, and calcium signaling molecules have been associated with SLE, which leads to hyperresponsive autoreactive T cells. Furthermore, in patients with SLE increased numbers of autoreactive Th17 cells have been documented, and Th17 cells appear to be responsible for tissue inflammation and damage. In addition, reduced numbers of Tregs as well as Tregs with an impaired regulatory function have been associated with SLE. The altered balance between the number of Tregs and Th17 cells in SLE may result from changes in the cytokine milieu that favors the development of Th17 cells over Tregs.

Keywords: systemic lupus erythematosus, T cells, autoimmunity, TCR signaling, Th17 cells, Tregs

INTRODUCTION

Systemic lupus erythematosus (SLE) is characterized by the presence of autoreactive antibodies against nuclear components, in particular, chromatin. Autoreactive B cells that produce pathogenic autoantibodies against nuclear components, such as double stranded DNA (dsDNA), nucleosomes, and histones, are central players in the pathogenesis of SLE (1). Autoantibodies can be detected years before the onset of clinical manifestations of the disease, which suggests a gradual loss of tolerance (2). Immune complexes of autoantibodies and chromatin deposit in various tissue, including the kidney, thereby triggering the activation of the complement system and subsequent influx of inflammatory cells (3). The vast majority of patients with SLE are female, which could be explained by a yet unknown mechanism involving the X-chromosome and/or the hormonal status (4). Prevalence of SLE varies from 20 to 150 cases per 100,000 individuals, with the highest occurrence reported in Brazil (3). To date, most patients with SLE are treated with non-specific immunosuppressive drugs and corticosteroids, which have severe side effects.

As outlined, autoantibodies in SLE are mainly directed against nuclear components, which are normally present in the nucleus inside the cell. The exposure of the immune system to released nuclear antigens in SLE patients may be explained by an aberrant apoptosis and/or impaired clearance of apoptotic cells. Apoptosis is a tightly controlled cellular program that is characterized by the breakdown of cellular components, which includes the fragmentation of chromatin. Normally, early apoptotic cells are swiftly cleared by phagocytes. However, in SLE, the process of apoptosis and/or the clearance of apoptotic material may be impaired, which could lead to the extracellular presence of chromatin triggering immune cells of the innate and adaptive immune system (5, 6). Especially, apoptotic microvesicles containing apoptosis-modified histones can be highly immunogenic through the activation of myeloid and plasmacytoid dendritic cells (DCs), and autoreactive B cells (7–12).

Normally, extracellularly present antigens ingested by antigen-presenting cells are presented in major histocompatibility complex class II molecules (MHC class II) to the T cell receptor (TCR) of CD4-positive T cells, thereby contributing to the activation of T cells. Certain lines of evidence suggest that T cells of patients with SLE are hyperresponsive compared to T cells from healthy individuals. The hyperresponsiveness of T cells in SLE may be due to changes in the signaling machinery downstream of the TCR. It has been described that autoimmunity toward chromatin in SLE depends on help of autoreactive T cells. In SLE, T cell function seems to be impaired, whereas the balance between regulatory T cells (Tregs) and Th17 cells appears to be disturbed (13–15), which will be the focus of this review.

T CELL ACTIVATION AND TCR SIGNALING IN HEALTHY INDIVIDUALS

Upon recognition of the antigen presented in MHC class II, the TCRs on the T cell will organize in the so-called immunological synapse. The TCR/CD3 complex, together with the co-receptor CD4, co-stimulatory molecules, and other signaling molecules are recruited to the center of the supramolecular activation cluster (SMAC) (16). The contact between the T cell and the APC is sustained through action of adhesion molecules, such as intracellular adhesion molecule 1 (ICAM-1) on the APC and lymphocyte function-associated antigen 1 (LFA-1) on the T cell. Most of the TCR/CD3 complexes and signaling molecules are present in lipid rafts already prior to engagement of the TCR. Upon binding to MHC class II, these lipid rafts serve as initiating spots of TCR signaling and fuse during the establishment of the immunological synapse (17, 18).

Antigen presented by an APC in the context of MHC class II molecules, the engagement of co-stimulatory molecules (e.g., B7 on APC and CD28 on T cells) and cytokines (e.g., IL-2) are the three signals that are required for full activation of T cells. In addition to the TCR, the co-receptor CD4 binds to MHC II. Intracellularly CD4 is associated with the lymphocyte-specific protein tyrosine kinase (Lck) that phosphorylates tyrosine residues in the immunoreceptor tyrosine-based activation motifs (ITAMs) of the TCR associated CD3 and zeta proteins (TCR ζ)

(19). Phosphorylated ITAMs serve as docking platforms for the Syk family tyrosine kinase Zeta-chain-associated protein kinase of 70 kDa (ZAP-70) (20). ZAP-70, in turn, phosphorylates the adaptor protein linker of activated T cells (LATs), which regulates the initiation of certain downstream-signaling pathways (21, 22). LAT can bind Ras GTP/GDP exchange factors, and thereby facilitates the activation of the Ras-mitogen-activated protein kinase (MAPK) pathway (23). LAT also serves as a docking protein for phospholipase C γ 1 (PLC γ 1), which ultimately results in the activation of protein kinase C (PKC) and the release of calcium from intracellular stores (24). Activation of MAPK or PKC, and increased intracellular calcium levels leads to activation of transcription factors, such as activator protein 1 (AP-1), nuclear factor κ B (NF κ B), and nuclear factor of activated T cells (NFAT). Activation of the aforementioned transcription factors leads to the expression of numerous genes, an altered cytokine production, and proliferation and differentiation of T cells. T cell activation is a reversible process. Tyrosine phosphatases, for example, counteract the activity of tyrosine kinases by binding to immunoreceptor tyrosine-based inhibition motifs (ITIMs) that are present in, for example, cytotoxic T-lymphocyte antigen 4 (CTLA-4) that competes with CD28 for binding to B7 (25).

ABERRANT TCR SIGNALING IN PATIENTS WITH SLE

In patients with SLE, an aberrant TCR signaling has been reported, which leads to hyperresponsiveness of T cells. Changes have been found in the expression of TCR ζ , the activation of intracellular spleen tyrosine kinase (Syk), calcium signaling, and various other kinase pathways (see Table 1; Figure 1) (26–28), which will be further detailed in the subsequent paragraphs.

TCR ζ EXPRESSION AND FUNCTION IN T CELLS IN SLE

Expression levels of TCR ζ are decreased in the majority of patients with SLE (28). In particular, TCR ζ mRNA levels are lower in SLE, which may be explained by unstable mRNA variants due to polymorphisms or alternative splicing in the 3' untranslated region (UTR) (30–32). In addition to reduced expression levels, phosphorylation of tyrosines in the ITAMs of TCR ζ seems to be reduced (29). Moreover, T cells of patients with SLE are less responsive to stimulation with anti-CD3 antibodies.

The downregulation of TCR ζ expression and activity, as outlined above, seems in contrast with the hyperresponsiveness of T cells in patients with SLE. However, it has been described that in T cells of patients with SLE the TCR ζ can be replaced by the more potent FC γ receptor (FC γ R) (46), as will be further discussed below. Furthermore, it has been shown that the inhibitory function of CTLA-4 is impaired in T cells of patients with SLE (47). Normally, CTLA-4 is associated with the tyrosine phosphatase SHP-2, which dephosphorylates TCR ζ , thereby disrupting TCR signaling (48). Due to the decreased expression of TCR ζ in patients with SLE, the regulatory function of CTLA-4 may be impaired. Finally, it has been suggested that impaired TCR ζ

TABLE 1 | Aberrant TCR-signaling components in SLE.

Component	Changes in SLE T cells	Reference
TCRζ	Decreased TCR ζ expression/ phosphorylation 3' UTR variants leading to instable versions of TCR ζ	Grammatikos et al. (26), Kytтарis et al. (27), Pang et al. (29), and Takeuchi et al. (28) Chowdhury et al. (30), Gorman et al. (31), and Tsuzaka et al. (32)
Syk	Replaces canonical ZAP-70 More potent signal transduction Increased expression: inability of CREM α to repress transcription	Krishnan et al. (33) and Tanaka et al. (34) Tanaka et al. (34) Ghosh et al. (35)
Calcium signaling	Increased recruitment of NFATc2 into the nucleus → Elevated expression of CD154 Enhanced nuclear import of CAMK IV → Elevated expression of CREM α	Kytтарis et al. (36) Juang et al. (37)
Other signaling components	LAT displaced from lipid rafts Aberrant phosphorylation of Erk	Abdoel et al. (38) Cedeno et al. (39) and Yi et al. (40)
Genes identified by GWAS	UBASH3A PP2AC TNFAIP3 SLAM	Diaz-Gallo et al. (41) Katsiari et al. (42), and Tan et al. (43) Graham et al. (44) Morel et al. (45)

signaling interferes with T cell selection processes in the thymus, which results in increased numbers of autoreactive T cells (34).

TYROSINE KINASE Syk IN T CELLS IN SLE

The observation that TCR ζ can be replaced by FC γ R in T cells of patients with SLE suggested a possible role for Syk tyrosine kinase in the pathogenesis of SLE (34), since FC γ R is known to interact with tyrosine kinase Syk rather than with the canonical tyrosine kinase ZAP-70. Syk is much more potent than ZAP-70 in phosphorylating its targets, which could explain the hyperresponsiveness of T cells in SLE. Indeed, Syk expression is massively increased in T cells of patients with SLE compared to healthy individuals, whereas ZAP-70 expression levels are similar (33). Furthermore, inhibition of Syk resulted in decreased phosphorylation, actin polymerization, and calcium responses in T cells of patients with SLE, and ameliorated skin and kidney disease in a mouse model for lupus (33, 49). Importantly, Grammatikos and colleagues showed that induced expression of Syk in T cells from healthy individuals leads to expression of inflammatory factors, such as IL-21 and CD44, which could be counteracted by silencing of Syk (26).

Two underlying mechanisms leading to an increased expression of Syk in T cells of patients with SLE have been identified. First, in T cells of patients with SLE increased levels of the transcription factor c-Jun drive the expression of Syk (50). Second, in SLE impaired binding of the transcriptional repressor cAMP responsive element modulator α (CREM α) in the promoter region of Syk has been shown, which is due to hypermethylation of the cAMP responsive element (35).

CALCIUM SIGNALING IN T CELLS IN SLE

During T cell activation PLC γ 1-mediated production of inositol triphosphate (IP3) leads to increased calcium levels in the cytosol. Subsequently, calcium bound to calmodulin enables the serine/threonine phosphatase calcineurin to dephosphorylate inactive cytoplasmic phosphorylated NFAT that then translocates to the nucleus. After stimulation with either anti-CD3 antibody or PMA/ionophore, the nuclear recruitment of NFATc2 is increased in T cells of patients with SLE compared to those of healthy controls (36). Furthermore, NFATc2 shows an increased association in the promoter of the gene encoding the co-stimulatory molecule CD154 in patients with SLE compared to healthy controls, which is associated with an increased CD154 expression (36). The increased expression of CD154 most likely contributes to the hyperresponsive phenotype of T cells in SLE. Expression of NFATc1 appears to be elevated in MRL/lpr mice, an experimental model for SLE, thereby explaining the increased CD154 expression (27). Interestingly, treatment of MRL/lpr mice with dipyridamole, a drug targeting the calcineurin–NFAT pathway, reduced CD154 expression on T cells, decreased T cell dependent antibody production, and improved clinical signs of nephritis (27).

Activated calmodulin can also activate calcium/calmodulin-dependent kinase IV (CAMK IV). Activated CAMK IV translocates from the cytoplasm into the nucleus and activates transcription factors, which includes the transcriptional repressor CREM α . Nuclear import of CAMK IV is increased in T cells in SLE, which could explain the increased activation of CREM α and subsequent suppression of the gene encoding IL-2 that is negatively regulated by CREM α . Notably, IL-2 is essential for a proper development of Tregs and Th17 cells (37) and will be further detailed in paragraphs about Th17 cells and Tregs.

OTHER T CELL SIGNALING MOLECULES IN SLE

As outlined, LAT plays a central role in activation of T cells. It has been reported that LAT expression is decreased in patients with SLE and LAT is not found in lipid rafts compared to T cells from healthy individuals (38). Consequently, activation of the MAPK pathway is impaired, and phosphorylation of Erk1/2 is decreased in SLE compared to controls (39). Furthermore, it has been shown that the LAT-dependent coupling of Grb to human son of sevenless (hSOS), which facilitates the activation of Ras, was reduced in T cells of patients with SLE compared to T cells from healthy controls (39). Other studies showed aberrancies in peripheral T cell tolerance in SLE, i.e., induction of anergy, through sustained

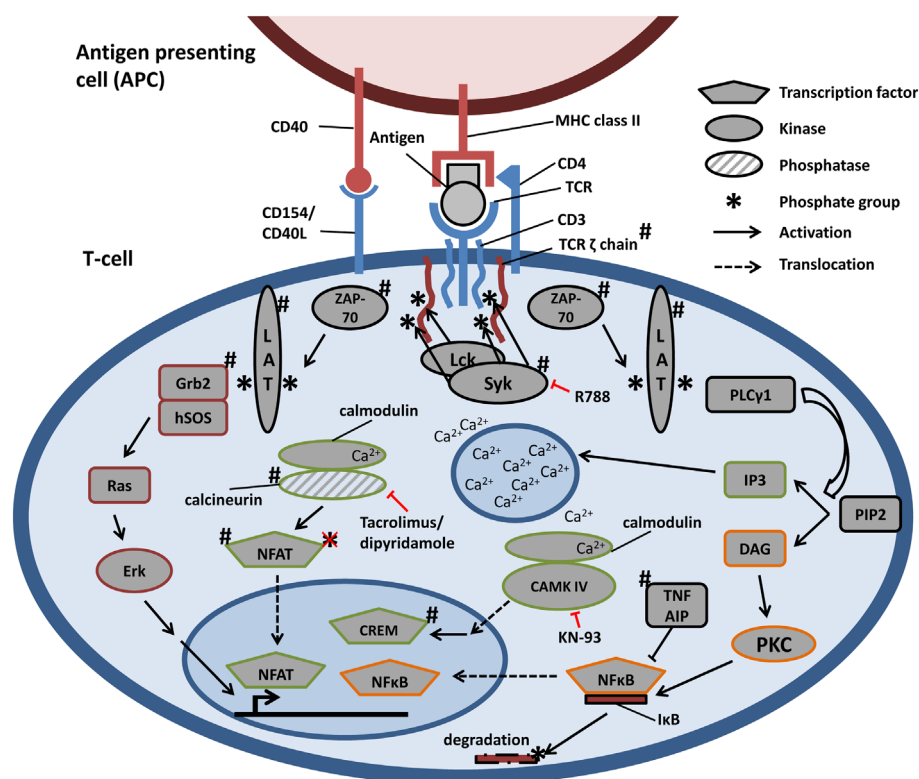


FIGURE 1 | Schematic representation of TCR-signaling pathways and aberrancies in SLE. Engagement of TCR, through the recognition of antigen in the context of MHC class II, triggers the assembly of TCR, CD3, and TCR ζ chains. TCR ζ is phosphorylated and recruits ZAP-70, which in turn phosphorylates LAT. LAT serves as docking protein and phosphorylation initiates the activation of Ras-Erk, calcium-dependent, and PKC-driven signaling pathways. All signals result in the activation of transcription factors, accumulating in the nucleus and influencing gene expression. *Signaling components described to be aberrantly regulated in SLE (see Table 1 and text). Therapeutic targets are depicted in red. Key: R788 is Syk inhibitor; KN-93 is CAMK IV inhibitor.

phosphorylation of Erk accompanied with an increased expression of the co-stimulatory molecule CD40L, thereby contributing to the persistent presence of autoreactive T cells (40).

Genome wide association studies (GWAS) revealed additional aberrancies in T cell signaling in SLE, which included a suppressor of T cell signaling called *UBASH3A* (41). Furthermore, SNPs in the *PPP2AC* gene have been associated with SLE (43). *PPP2Ac* expression in T cells of patients with SLE is increased, thereby reducing the production of the cytokine IL-2 that is essential for the induction of Tregs and Th17 cells (42). *PP2A* dephosphorylates and inactivates cAMP response element-binding protein (CREB), a transcriptional activator of IL-2 (51). Additionally, variants in the tumor necrosis factor alpha protein 3 (*TNFAIP3*) gene have been associated with SLE (44). *TNFAIP3* encodes for a zinc finger protein that negatively regulates the NF κ B pathway, which is a central player in activation of immune cells and inflammatory processes (52).

Th17 AND Tregs T CELL SUBSETS IN THE PATHOGENESIS OF SLE

T cells can be divided into multiple subsets according to their phenotype and function. Tregs are important CD4-positive T cells that function in peripheral T cell tolerance by inhibition of

autoreactive T cells. Tregs can exert their tolerogenic functions via direct cell-cell contact or by the release of immunosuppressive factors, such as transforming growth factor β (TGF β) and IL-10, whereas they are identified by the transcription factor FoxP3 (53). Reduced numbers of Tregs and impaired function of Tregs have been associated with SLE (54, 55).

Th17 cells constitute a subset of CD4-positive T cells that have been identified a decade ago. Development of Th17 cells requires TGF β and IL-6, and they are identified by the specific transcription factor ROR γ t, and their characteristic production of IL-17 (56, 57). Th17 cells have been associated with chronic infection and autoimmune diseases including SLE (15).

Notably, in addition to Tregs and Th17 cells, double negative T cells, lacking both CD4 and CD8 expression, and T cells expressing the gamma and delta chain of TCR appear to play a role in the pathogenesis of SLE (58–61). However, we will focus in this review on Th17 cells and Tregs in SLE as further detailed in the subsequent paragraphs.

Th17 CELLS IN SLE

Th17 cells seem to play a role in the pathogenesis of SLE. Prior to the discovery of Th17 cells, it was believed that Th1 and Th2

cells were the central players in establishing autoimmunity reactions and tissue damage. For SLE, this view changed with the identification of high levels of IL-17 and Th17 cells in patients with SLE and in mouse models for SLE (62, 63). IL-17 and Th17 cells are increasingly present in BXD2 mice that show a lupus-like autoimmune phenotype and were implicated to contribute to the formation of germinal centers and subsequent production of pathogenic antibodies (62). In other mouse models of SLE, the *Ets* knockout mouse (*Ets*^{-/-}) and the New Zealand Black (NZB) × SWR F1 cross (SNF1 mice), increased levels of Th17 cells and IL-17 seem to contribute to the inflammation of kidneys, i.e., glomerulonephritis (64, 65).

Increased IL-17 production in SLE may be explained by over-active costimulation via SLAM. Polymorphisms in the cluster of SLAM encoding genes have been associated with SLE (45). Expression of *SLAMF3* and *SLAMF6* is enhanced in T cells in SLE, whereas costimulation via SLAM seems more effective compared to costimulation via CD28 in initiating the transcription of the *IL-17* encoding gene (66). Costimulation mediated by *SLAMF3*/*SLAMF6* results in the recruitment of ROR γ t and NFAT to the promoter region of the *IL-17* encoding gene, thereby enhancing transcription of IL-17 compared to costimulation via CD28 (67). Importantly, silencing of SLAM or SLAM-associated protein (SAP) leads to a reduced production of IL-17 (66). As outlined, calcium signaling pathways, which promote the translocation of NFAT from the cytoplasm to the nucleus, are hyperactive in SLE T cells. This probably leads to higher levels of activated NFAT, which together with increased SLAM signaling drive the transcription of *IL-17* and promote Th17 development.

The transcription factor STAT3 is also involved in the development of Th17. Expression of STAT3 is increased in T cells in SLE, whereas inhibition of STAT3 leads to decreased T cell migration and delayed onset of autoimmunity in lupus prone mice (68, 69).

In addition to Th17 cells, double negative (CD4⁻, CD8⁻) T cells can produce IL-17 in SLE (58). Notably, the number of double negative T cells is increased in patients with SLE compared to healthy individuals. Taken together, an increased level of IL-17 in patients with SLE establishes an autoreactive and inflammatory environment that can lead to tissue damage.

REGULATORY T CELLS IN SLE

As mentioned, Tregs are important cells in establishing peripheral T cell tolerance. Therefore, the number of Tregs and function of Tregs have been studied extensively in SLE. The majority of Tregs cells are characterized by the expression of the transcription factor *Foxp3* and high expression levels of the IL-2 receptor alpha chain (CD25). The development of Tregs depends on the presence of IL-2 and TGF β . Currently, different subsets of Tregs have been described; however, we will focus in this review on *Foxp3*-positive cells.

The role of aberrancies in the number of Tregs and/or function of Tregs in the pathogenesis of SLE remains controversial. Some studies demonstrated a decreased number of Tregs in patients with SLE (54, 55), which could be explained by an increased susceptibility to Fas-induced cell death (55). By contrast, other reports demonstrate that the number of Tregs is similar for

patients with SLE and controls (70, 71). In our opinion, the variation in outcome of different studies that address Tregs in SLE could be explained by different methods of isolation and characterization.

Regarding the suppressive function of Tregs in SLE, different claims have been published as well. Several reports demonstrate that the suppressive function of Tregs in SLE is impaired (54, 70, 72). Other reports claim that the suppressive function of Tregs in SLE is not impaired, but that autoreactive effector T cells in SLE are less susceptible to suppression by Tregs (71). However, it also has been demonstrated that Tregs from healthy controls are able to suppress effector T cells of patients with SLE (72). Taken together, Tregs seem to play a role in the pathogenesis of SLE.

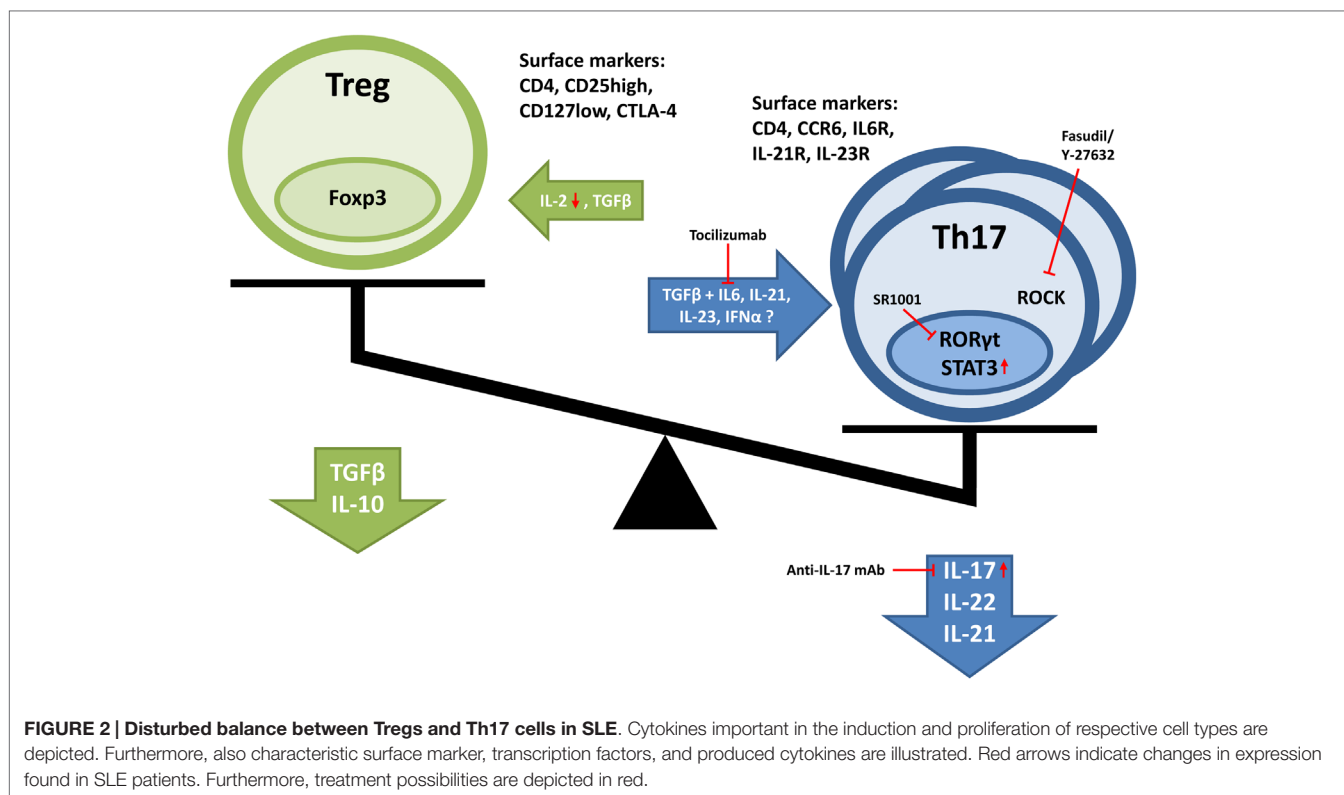
DISTURBED BALANCE BETWEEN Tregs AND Th17 CELLS IN SLE: A MATTER OF CYTOKINES?

As outlined above, there is strong evidence for a disturbed balance between Th17 cells and Tregs in patients with SLE. However, the mechanisms underlying alterations in numbers and/or function of Th17 and Tregs in SLE are only partially understood, but may involve the overall cytokine milieu (see Figure 2).

The growth factor TGF β plays an important role in the development of both Th17 cells and Tregs. TGF β promotes the differentiation of naïve T cells into Tregs. Furthermore, TGF β induces the expression of *Foxp3* in $\gamma\delta$ T cells and stimulates $\gamma\delta$ T cells to exert suppressive functions (61). For the development of Th17 cells, the combined action of TGF β and IL-6 is required, whereas Treg development depends on IL-2 and TGF β . Interferon type I (IFN type I) levels, in particular IFN- α , are increased in patients with SLE (73, 74). IFN- α is primarily produced by plasmacytoid DCs (pDCs) upon recognition of nucleic acids by toll-like receptor 7 and 9 (75). IFN- α contributes to the maturation of myeloid DCs that can activate autoreactive T cells in patients with SLE. It has been suggested that IFN- α also promotes the development of Th17 cells (76). It has been shown that IFN- α triggers the production of IL-6 by myeloid DCs, whereas IL-6 is required for the development of Th17 cells (77). Moreover, it has been suggested that IFN- α impairs the suppressive function of Tregs in SLE. Importantly, in the presence of IFN- α producing DCs, Tregs of SLE patients as well as Tregs of healthy controls were not capable of suppressing T effector cells (78).

IL-2 is another cytokine that is crucial for the development of both Tregs and Th17 cells (79, 80). IL-2 is mainly produced by CD4⁺ T cells, and it is involved in the proliferation and survival of activated effector T cells. However, IL-2 or IL-2 receptor-deficient mice models show autoimmune phenotypes (81, 82), which may be explained by reduced numbers of Tregs that require IL-2 for proper development and function (83). As outlined above, production of IL-2 in patients is impaired due to the concerted action of FC γ R, Syk, CREM α , and CREB (51, 84). Interestingly, increasing levels of IL-2 restore the suppressive function of Tregs in SLE when tested *in vitro* (72).

Regulatory T cells as well as Th17 cells have been shown to possess a certain degree of plasticity. It has been described that



mouse Foxp3⁺ Tregs are able to transdifferentiate into Th17-like cells due to the action of IL-6 in the absence of TGFβ (85–87). Also in human, Tregs are able to adapt a Th17-like phenotype, which is accompanied with the production of IL-17 (88). It appears that Tregs that produce IL-17 can retain their suppressive function until they are triggered by IL-6 and IL-1β (89). Taken together, the cytokine milieu in patients with SLE may disturb the balance between Th17 cells and Tregs in favor of the Th17 cells, thereby explaining autoimmunity and inflammation. Dynamic changes in the cytokine milieu may transiently disturb the balance between Th17 cells and Tregs, thereby driving flares of active disease in SLE (90, 91).

EFFECT OF HIGH SALT DIET ON THE BALANCE BETWEEN TREGS AND Th17 CELLS

Recently, it has been described that high salt intake may induce the development of Th17 cells in autoimmune diseases (92, 93). The development of Th17 cells from naïve CD4⁺ T cells was enhanced by increased sodium chloride (NaCl) concentrations in the culture medium. Furthermore, increasing the dietary intake of NaCl in an autoimmune disease mice model (experimental autoimmune encephalomyelitis, EAE) increases autoimmune features of the model. However, high salt diet in mouse models for SLE did not affect SLE disease activity (94). It has been described that NaCl activates the MAPK pathway leading to the activation of serum/glucocorticoid-regulated kinase 1 (SGK1). SGK1, in turn, suppresses the activity of Foxo1, a repressor of

IL-23 expression (93). Therefore, increased NaCl concentrations result in increased production of IL-23, which contribute to the development and maintenance of Th17 cells. Increased expression levels of SGK1 have been described in patients with SLE as well (95). Interestingly, high salt intake has been correlated with a decreased effectiveness of treatment with glucocorticoids in a Chinese cohort of patients with SLE (96).

TREATMENT OPTIONS TARGETING T CELLS IN SLE

The increasing insight into the disease mechanisms of SLE allows for the development of more disease-specific drugs targeting, for example, the aberrant signaling mechanisms in T cells or the balance between Th17 cells and Tregs. Current treatment of SLE includes anti-inflammatory agents, anti-malarial drugs, glucocorticoids, and immunosuppressive medicines (3). Considering the central role of Syk in the aberrant signaling in T cells in SLE, currently specific Syk inhibitors are under development. The compound R788 inhibited the onset of kidney-related disease manifestations in mouse models for SLE (49). Furthermore, R788 was successful in the treatment of rheumatoid arthritis in a phase II clinical trial, which could encourage a clinical trial of R788 in patients with SLE as well (97).

It is well documented that inhibitors of the calcineurin–NFAT pathway, such as tacrolimus or dipyridamole decrease the production of inflammatory cytokines and reduce clinical manifestations in SLE (27). Furthermore, it has been described

that blocking of CAMK IV, using the pharmacological inhibitor KN-93 suppresses production of pro-inflammatory cytokines TNF α and IFN γ , and improves proteinuria and nephritis in the MRL/lpr mouse model (98).

Targeting of co-stimulatory or adhesion receptors on T cells is another treatment option. Since CD40 is expressed at higher levels on T cells of patients with SLE compared to those of healthy controls, inhibition of either CD40 or its ligand CD40L may reduce the activation of autoreactive T cells (40). CD44 expression on T cells of patients with SLE is enhanced as well. CD44 is involved in the adhesion of T cells and has been associated with increased cell migration toward the kidneys, thereby contributing to inflammation and damage of the kidney (99). Engagement of CD44 leads to the activation of Rho kinase (ROCK) and production of IL-17. Therefore, inhibitors of ROCK could disrupt CD44-mediated signaling in T cells in SLE (100). Abatacept is a CTLA-4 immunoglobulin fusion protein that is used to compete with CD28 for binding to B7 proteins, thereby reducing activation of autoreactive T cells.

Restoration of the balance between Th17 cells and Tregs in patients with SLE could be achieved by manipulation of the cytokine milieu in such a way that the development of Tregs is favored over Th17 cells. A strategy could include the blocking of IL-17 or IL-23, cytokines important for the development of Th17 cells. However, blocking IL-17 alone showed a worsening of the disease phenotype in mouse models (101, 102). More encouraging is the blocking of the IL-6 receptor using a monoclonal antibody, tocilizumab, which showed promising results in clinical phase I studies (103). Moreover, the inhibition of the main transcription factor involved in the development of Th17 cells, ROR γ t, using

a synthetic molecule (SR1001) also appears to be beneficial in blocking the differentiation of Th17 cells (104).

CONCLUDING REMARKS

We summarized multiple mechanism and pathways impaired in T cells from patients with SLE. A note of caution should be made, since in SLE, there is no general and/or complete picture regarding its pathogenesis when comparing individual patients. So, not all aberrancies in T cell signaling and disturbances in Th17 cell/Tregs as described in this review are present in all patients with SLE. Nevertheless, the signaling cascades emerging from the TCR and ultimately leading to changes in the expression of numerous genes play a key role in the phenotype of T cells in SLE. In general, aberrancies in TCR signaling lead to a hyperresponsive state of T cells in SLE. Moreover, aberrancies in TCR signaling may affect selection processes in the thymus, thereby impairing central tolerance. Small molecule inhibitors specific for certain key signaling molecules (e.g., Syk and CAMK IV) have been developed and show promising results in pre-clinical as well as in clinical studies. The interplay between Tregs, Th17 cells, and other cell subsets is complex and only in part understood. Restoring a healthy balance between Tregs and Th17 cells in patients with SLE is not a straight forward therapeutic option yet, but an interesting research goal that may be translated into clinical practice in a later phase.

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